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Original article

Prognosis of adult idiopathic inflammatory myopathy-associated interstitial lung disease: a retrospective study of 679 adult cases

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Abstract

Objectives. Few studies have investigated the prognostic factors for idiopathic inflammatory myopathy-associated interstitial lung disease (IIM-ILD) across different clinical/serological phenotypes.

Methods. We conducted a retrospective analysis of patients diagnosed with IIM between January 2012 and December 2017.

Results. Of the 760 IIM cases registered, 679 adult cases were included in this study. ILD was present in 508 cases, and the presence of ILD in the clinically amyopathic DM, DM and PM groups was 92.7, 73.6 and 55.1%, respectively ($P < 0.01$). The prevalence of ILD in the anti-synthetase antibody (ASA)$^+$-IIM group was higher than that in ASA$^-$-IIM group (95.2 *vs* 72.4%, $P < 0.01$); no such difference was found between the anti-histidyl-tRNA synthetase (Jo-1)$^+$-IIM and Jo-1$^-$ASA$^+$-IIM groups (93.0 *vs* 98.5%, $P > 0.05$). The prevalence of ILD in the melanoma differentiation-associated protein-5 (MDA-5)$^+$-IIM group was higher than that in MDA-5$^-$-IIM group (97.8 *vs* 72.1%, $P < 0.01$). Among adults with IIM, men with concurrent ILD, who were older than 50 years, were most likely to die. No significant difference was found in the all-cause mortality rates between DM-ILD and clinically amyopathic DM-ILD groups (33.3 *vs* 23%, $P > 0.05$), although both were higher than that in PM group (13.2%, $P = 0.01$ and $P < 0.05$, respectively). No difference was found in the all-cause mortality rates between MDA5$^-$ASA$^-$-IM-ILD and MDA5$^-$ASA$^+$-IM-ILD groups (17.2 *vs* 12.8%, $P > 0.05$), and both were lower than that in MDA5$^+$ASA$^-$-IM-ILD group (33.7%, $P < 0.05$).

Conclusion. The prevalence of ILD in IIM and the prognosis of IIM-ILD patients may vary depending on the statuses of the ASA and MDA-5 antibodies.

Key words: idiopathic inflammatory myopathy, interstitial lung disease, myositis autoantibody, anti-synthetase antibody, melanoma differentiation-associated protein-5 antibody, prognosis

Rheumatology key messages

- The ASA$^+$ and/or MDA-5$^+$ IIM patients were more likely to develop ILD.
- The presence of ILD in adult IIM patients leads to a 2.2-fold increased risk of death.
- The MDA-5$^+$ IIM-ILD patients demonstrated the worst prognosis regardless of the ASA positivity.

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Introduction

With the recent application of myositis autoantibody profiling, myositis-specific antibodies (MSAs) have been suggested as a useful prognostic factor [1]. Therefore, the clinical/serological classification of idiopathic inflammatory myopathy (IIM), based on clinical manifestations and myositis autoantibody profiles [1–3], may replace the previous clinical classification of IIM as DM, PM, clinically amyopathic DM (CADM) and JDM.

The determination of serum myositis autoantibody profiles has been used with an increasing frequency at

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our hospital since 2012. However, few studies have examined the prognostic factors for IIM associated with interstitial lung disease (IIM-ILD) across different clinical-serological phenotypes. We conducted this retrospective analysis of patients with IIM admitted to our hospital between January 2012 and December 2017 in combination with their MSA results.

Methods

Patients

The electronic medical records at Peking Union Medical College Hospital were searched using 'myositis', 'dermatomyositis' and 'polymyositis' for the time period from January 2012 to December 2017. This search identified 760 patients diagnosed with IIM according to the 1975 Bohan and Peter criteria [4, 5]. Among these, 712 patients who had complete medical records, radiological imaging data and follow-up information were retrospectively enrolled in this study. All patients with IIM-ILD underwent chest high-resolution CT (HRCT). They were followed up every 1–6 months, depending on disease activity and severity. The final follow-up point was 30 June 2018. The mean follow-up period was 24 months, ranging from 0.5–77 months. Follow-up information was obtained through outpatient follow-up records or telephone conversations.

Survival time was defined as the time from initial diagnosis of IIM to death or the final follow-up point. The following information was analysed: age, sex, clinical manifestations, serological results, radiological findings, pathological manifestations, treatments and outcomes. All chest HRCT images were reviewed by one radiologist and one respiratory physician, who were blinded to each other's interpretations.

Associated autoantibodies

Blood tests were performed at the clinical laboratory department at Peking Union Medical College Hospital, except for myositis autoantibody profiles, which were measured at Dean Diagnostic Technology Co., Ltd, Beijing, China. The ANA profile for 18 ANAs and myositis autoantibody profiles were assessed by an immunoblotting assay using an EUROIMMUN kit (EUROIMMUN Medizinische Labordiagnostika AG. Address: Seekamp 31, D-23560, Lübeck, Germany) [6]. Anti-histidyl-tRNA synthetase (anti-Jo-1), anti-threonyl-tRNA synthetase (anti-PL7), anti-alanyl-tRNA synthetase (anti-PL12), anti-glycyl tRNA synthetase (anti-EJ), anti-isoleucyl-tRNA synthetase (anti-OJ) and anti-melanoma differentiated-associated protein-5 (MDA-5) were included in the myositis autoantibodies profile.

Defining CADM, antisynthetase syndrome and ILD

In this study, CADM was defined as a subgroup of patients with amyopathic and/or hypomyopathic DM [7]. These patients showed characteristic rashes and/or biopsy-confirmed cutaneous manifestations of DM, without clinical evidence of proximal muscle weakness and normal serum creatine kinase. The diagnosis of antisynthetase syndrome (ASS) was made according to Connors' diagnostic criteria [8], which included the presence of an anti-aminoacyl tRNA synthetase antibody plus one or more of the following clinical features: RP, arthritis, ILD, fever (not attributable to another cause) or mechanic's hands (thickened and cracked skin on hands, particularly at the fingertips). ILD was defined by the presence of hallmark manifestations on chest HRCT [9, 10]. The chronological relationship between IIM and ILD was defined as follows: if the diagnoses of ILD and IIM were >3 months apart, then it was defined as ILD occurring before or after IIM; if the duration between these diagnoses was <3 months, then it was defined as concurrent ILD and IIM. The characteristic IIM-associated rashes include heliotrope erythema, Gottron papules and Gottron macules.

This study was approved by the ethics committee of the Peking Union Medical College Hospital (JS-1127, ZS-1058) in accordance with the principles of the Declaration of Helsinki. All patients and/or their relatives provided written informed consent.

Statistical analysis

The data were analysed using the Statistical Product and Service Solutions (SPSS, SPSS Inc., Chicago, IL, USA) version 23.0 software package. GraphPad Prism (GraphPad Software, San Diego, CA, USA) version 7.0 was used for graphing. Quantitative variables are presented as the means (S.D.), and categorical data are presented as frequencies and percentages in the text and figures. The *t*-test or rank sum test was used for measured data, and the χ^2 test was used for count data. The difference was statistically significant when $P < 0.05$. The log-rank test was used to compare the survival rates of different subgroups, and Kaplan–Meier survival curves were plotted. Cox regression models were used to identify factors associated with mortality for IIM and IIM-ILD. The variables selected via univariate analysis were finally assessed by multivariate analysis.

Results

This study consisted of 221 males and 491 females, with a mean (S.D.) age of 49.4 (12.7) years (range 18–78 years) for adult cases and a mean age of 10.7 (4.5) years (range 1–17 years) for juvenile cases. Of the 712 patients, 363 (51%), 138 (19.4%), 178 (25%) and 33 (4.6%) cases were included in the DM, PM, CADM and JDM groups, respectively. Among these, 679 adult IIM patients were further analysed in detail in our study, of which 363 (53.5%), 138 (20.3%) and 178 (26.2%) cases were included in the DM, PM and CADM groups, respectively. No significant difference was found in the age distribution among the subgroups of adults with IIM. The median follow-up time was 21 months (range 0.5–

73 months), and 57 patients (8.4%) were lost to follow-up.

IIM-ILD with different clinical subtypes of IIM

Of the 679 adult patients with IIM, 508 (74.8%) were complicated with ILD, as confirmed by chest HRCT. Furthermore, 374 cases (73.6%) had evidence for ILD at the time of IIM diagnosis, 95 cases (18.7%) were diagnosed with ILD before IIM, and 39 cases (7.7%) were diagnosed with ILD after the diagnosis of IIM was established. The presence of ILD in the DM ($n = 363$), PM ($n = 138$) and CADM ($n = 178$) groups was 73.6, 55.1 and 92.7%, respectively, and the differences among these groups were significant ($\chi^2 = 59.06$, $P < 0.01$).

The general characteristics of the enrolled 679 adults IIM cases is summarized in supplementary Table S1, available at *Rheumatology* online.

IIM-ILD with different clinical-serological subtypes of IIM

The anti-synthetase antibody (ASA) and MDA-5 MSAs are closely associated with the occurrence of ILD in IIM patients [9]. Therefore, patients testing positive for ASA and MDA-5 antibodies in their myositis autoantibody profiles were further analysed. All 679 adult patients were categorized based on the 18 items of the ANA profile, and 67 were tested positive for the Jo-1 antibody. (No further examination of myositis autoantibody profiles was performed for these patients.) Of the remaining 612 patients, 301 patients (48%) underwent myositis autoantibody profile examination. A further analysis of 368 patients, including the 301 patients who underwent the myositis autoantibody profile examinations and the 67 patients who were tested positive for the Jo-1 antibody according to the ANA profile analysis, revealed that 304 (82.6%) of the patients were complicated with ILD. The presence of ILD in the 165 ASA-positive (ASA^+)-IIM cases was higher than that in the 203 ASA-negative (ASA^-)-IIM cases (157/95.2 *vs* 147/72.4%, $\chi^2 = 32.75$, $P < 0.01$). A total of 100 (60.6%) of the 165 ASA^+-IIM cases were positive for the anti-Jo-1 antibody, and the presence of ILD among these patients was 93.0%, which did not differ from the rate among the other ASA^+-IIM cases (93.0 *vs* 98.5%; $\chi^2 = 2.55$, $P = 0.11$). Of the 203 ASA^--IIM cases, 85 (41.9%) were MDA-5-positive (MDA-5^+)-IIM cases, 97.6% of which were complicated with ILD. This rate was higher than the presence of ILD among the remaining 118 cases of MDA-5-negative (MDA-5^-)-IIM cases (54.2%; $\chi^2 = 46.61$, $P < 0.01$) (supplementary Figs S1 and S2, available at *Rheumatology* online).

Of the 301 patients who underwent myositis autoantibody profiling, 241 (80.07%) were complicated with ILD. Based on the ASA and MDA-5 antibody profiles, these patients were further divided into four subgroups: an $ASA^+/MDA5^-$ group (90 cases; 29.9%), $ASA^+/MDA5^+$ group (8 cases; 2.7%), $ASA^-/MDA5^+$ group (85 cases; 28.2%) and $ASA^-/MDA5^-$ group (118 cases; 39.2%). All patients in the $ASA^+/MDA5^+$ group had ILD. The rates of ILD in $ASA^+/MDA5^-$ (86 cases; 95.6%) and $ASA^-/MDA5^+$ (83 cases; 97.6%) groups did not significantly differ ($\chi^2 = 0.12$, $P = 0.73$), but both were higher than that in the $ASA^-/MDA5^-$ group (64 cases; 54.2%) ($\chi^2 = 43.35$, $P < 0.01$; $\chi^2 = 46.61$, $P < 0.01$, respectively).

Prognosis analysis for IIM across different clinical phenotypes

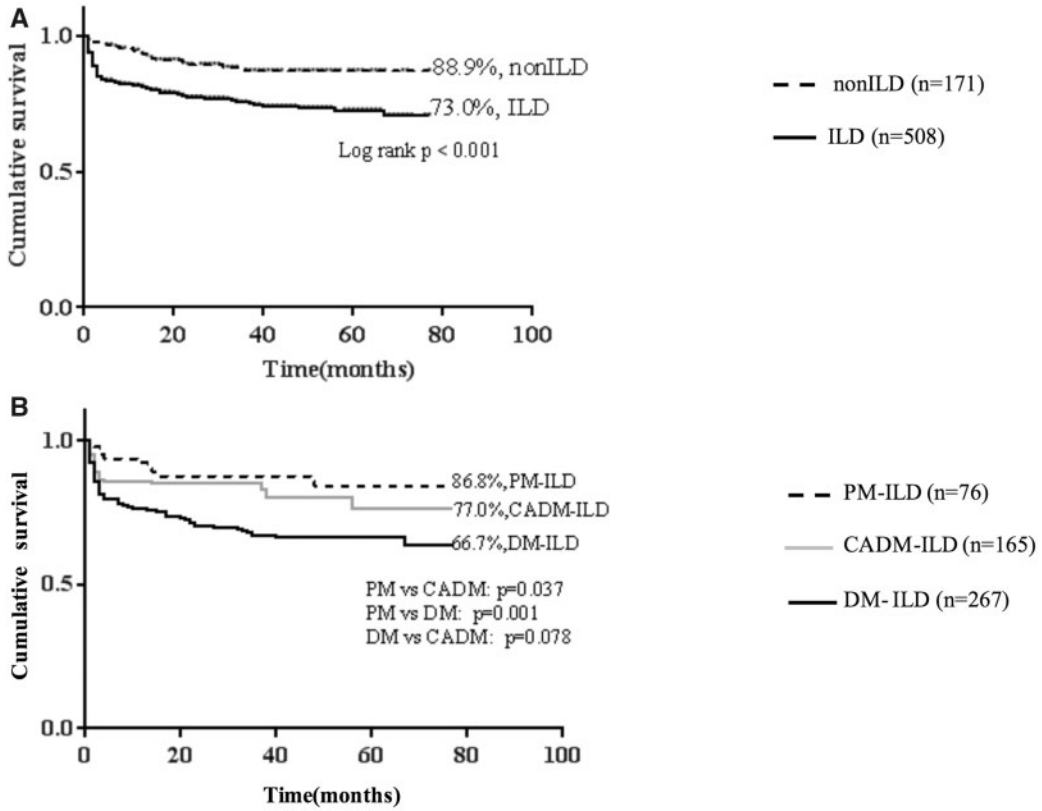
The overall mortality rate in this study was 22.9% (156/679 cases). A total of 69.8% (109/156 cases) of the patients died within 6 months after diagnosis. The all-cause mortality rates of the DM, PM and CADM groups were 28.4% (103/363), 10.1% (14/138) and 21.9% (39/178), respectively. No difference was found with regard to the all-cause mortality rates between the DM and CADM groups ($\chi^2 = 2.58$, $P = 0.11$), and both rates were higher than that of the PM group ($P < 0.01$).

To identify the prognosis-related factors for adult IIM, 679 adult IIM patients were further divided into a survival group and a death group. The effects of onset age, sex, and concurrent ILD or tumours on the survival rate were evaluated using a log-rank test. The results revealed that the average age of the patients who died [53.5 (11.1) years] was higher than that of the survivors [48.2 (12.9) years; $t = 4.595$, $P < 0.01$], and the onset age was no less than 50 years. Furthermore, male sex and concurrent ILD were risk factors for IIM-related death (Table 1). A Cox regression analysis (Table 1) showed that an onset age of no less than 50 years, male sex and concurrent ILD were independent risk factors for death in adults with IIM. The presence of ILD increased the risk of death 2.2-fold ($P < 0.001$). Fig. 1A shows the Kaplan–Meier survival curves for the IIM-ILD and non-IIM-ILD cases. The mortality rates of the DM-associated ILD (DM-ILD) group and the CADM-associated ILD (CADM-ILD) group were higher than those of the PM-associated ILD (PM-ILD) group. No difference was found with regard to the mortality rate between the CADM-ILD and DM-ILD groups (Fig. 1B).

Prognostic analysis of IIM cases positive for ASA

The 165 ASA^+-ILD patients were divided into a survival group and a death group. The effects of onset age, sex, concurrent tumours, concurrent ILD, classical skin lesions of DM, mechanic's hand, joint pain, muscle involvement, mediastinal/subcutaneous emphysema and anti-Jo-1 antibody on survival were analysed via the log-rank test. The variables associated with $P < 0.05$ in the log-rank test were selected for inclusion in the multivariate Cox regression analysis. An onset age of no less than 50 years old, concurrent tumours and mediastinal/subcutaneous emphysema were independent risk factors for death in the ASS group. The presence of joint pain in the ASS survival group was higher but not significantly higher than that in the death group. Concurrent ILD, mechanic's hand and Jo-1 antibodies were not prognostic factors in the ASS cases (Table 2).

FIG. 1 Kaplan–Meier survival curves of idiopathic inflammatory myopathy patients with different clinical phenotypes



(**A**) Kaplan–Meier survival curves of patients with idiopathic inflammatory myopathy (IIM) with *vs* without interstitial lung disease (ILD): patients who were diagnosed with IIM-ILD had a significantly lower survival rate than did those diagnosed with IIM without ILD (non-ILD) (log-rank, $P < 0.001$). (**B**) Kaplan–Meier survival curves of patients with DM, PM and clinically amyopathic DM (CADM) associated with ILD (DM-ILD, $n = 267$; PM-ILD, $n = 76$; and CADM-ILD, $n = 165$): Patients who were diagnosed with DM-ILD and CADM-ILD had significantly lower survival rates than did those diagnosed with PM-ILD (log-rank, $P = 0.001$ and $P = 0.037$, respectively). There was no significant difference in the survival time between DM-ILD patients and CADM-ILD patients (log-rank, $P = 0.078$).

TABLE 1 Univariate and multivariate models of death in adult IIM patients

Variables	Univariate log rank analysis				Multivariate Cox analysis			
	Living ($n = 523$)	Died ($n = 156$)	χ^2	*P*-value	Hazard atio	Lower (95% CI)	Upper (95% CI)	*P*-value
Age, ≥50 years (*n*/%)	226/43.2	98/62.8	25.67	<0.001	2.2	1.6	3.1	<0.01
Males (*n*/%)	147/28.1	58/37.4	5.32	0.02	1.4	1.0	2.0	0.03
Complicated with ILD (*n*/%)	371/70.8	137/88.4	19.62	<0.001	2.7	1.7	4.4	<0.01
With malignancy (*n*/%)	33/6.3	13/8.4	0.25	0.61				

ILD: interstitial lung disease.

Prognostic analysis of patients with IIM who tested positive for MDA-5 antibodies

A total of 93 MDA-5$^+$ cases were divided into survival and death groups. The effects of the onset age, sex, concurrent ILD, classical skin lesions of DM, mechanic's hand, joint pain, muscle involvement and mediastinal/subcutaneous emphysema on survival were analysed via a log-rank test (Table 3). The variables associated with $P < 0.05$ in the log-rank test were selected for the inclusion in the multivariate Cox regression analysis (Table 3). Age of onset of >50 years was an independent risk factor for death in this group, and the occurrence of the classical skin lesions of DM was a prognostic

Table 2 Univariate and multivariate models of death in anti-synthetase syndrome patients

Variables	Univariate analysis					Multivariate Cox analysis			
	Living ($n = 141$)	Died ($n = 24$)	t	χ^2	P-value	Hazard ratio	Lower (95% CI)	Upper (95% CI)	P-value
Age, years [mean (S.D.)]	49.2 (13.3)	57.0 (12.4)	2.71	–	0.01				
Age $n \geq 50$ years (n/%)	70/49.6	17/70.8	–	4.35	0.04	2.69	1.09	6.64	0.03
Males (n/%)	40/28.4	8/33.3	–	0.31	0.58				
Rash (n/%)	78/55.3	13/54.2	–	0.01	0.92				
Myositis (n/%)	71/50.4	15/62.5	–	0.55	0.46				
Complicated with ILD (n/%)	134/95.0	23/95.8	–	0.04	0.84				
Arthragia (n/%)	71/50.4	7/29.2	–	4.16	0.04				
Mechanic's hand (n/%)	53/37.6	9/37.5	–	0.01	0.92				
Pulmonary hypertention (n/%)	12/8.5	4/16.7	–	1.04	0.31				
Pneumomediastinum	2/1.4	6/25	–	39.02	<0.01	16.27	5.90	44.90	<0.01
Anti-Jo-1 positivity (n/%)	85/60.3	15/62.5	–	0.04	0.84				
With malignancy (n/%)	3/2.1	4/16.7	–	9.34	<0.01	5.27	1.72	16.15	<0.01

ILD: interstitial lung disease; JO-1: anti-histidyl-tRNA synthetase.

Table 3 Univariate and multivariate models of death in MDA-5$^+$ IIM patients

Variables	Univariate analysis					Multivariate Cox analysis			
	Living ($n = 63$)	Died ($n = 30$)	t	χ^2	P-value	Hazard ratio	Lower (95% CI)	Upper (95% CI)	P-value
Age, years [mean (S.D.)]	46.8 (10.9)	54.4 (11.3)	−3.12	–	<0.01				
Age, ≥50 years (n/%)	29/46.0	24/80	–	10.26	<0.01	4.15	1.67	10.31	<0.01
Males (n/%)	39/61.9	20/66.7	–	0.22	0.64				
Rash (n/%)	61/96.8	27/90.0	–	3.81	0.05	0.24	0.07	0.80	0.02
Myositis (n/%)	48/76.2	22/73.3	–	0.24	0.63				
Complicated with ILD (n/%)	61/96.8	30/100	–	0.77	0.38				
Arthragia(n/%)	39/61.9	14/46.7	–	2.64	0.10				
Mechanic's hand (n/%)	27/42.9	10/33.3	–	0.83	0.36				
Pneumomediastinum	10/15.9	4/13.3	–	0.12	0.73				

MDA-5: melanoma differentiated-associated protein-5; IIM: idiopathic inflammatory myopathy; ILD: interstitial lung disease.

protective factor in this group ($P < 0.05$), but concurrent ILD was also not a prognostic factor in the MDA-5$^+$ cases.

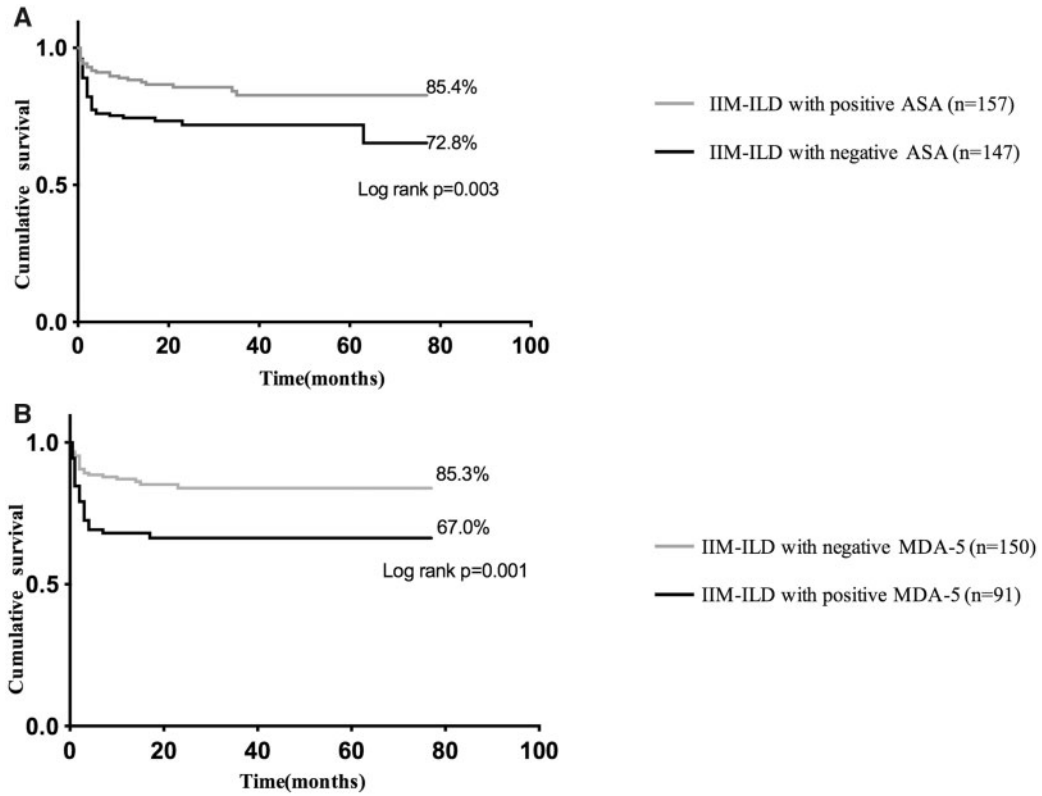
Prognostic analysis for patients with IIM-ILD and different ASA and MDA-5 antibodies

A total of 304 patients with IIM-ILD underwent ASA detection, including 157 ASA$^+$-IM-ILD cases and 147 ASA$^-$-IIM-ILD cases. The ASA$^+$ patients had a lower mortality rate than those negative for ASA [14.6 *vs* 27.2%, respectively; odds ratio (OR) 0.46, 95% CI: 0.26, 0.81]. The Kaplan–Meier curves for mortality in the ASA$^+$ and ASA$^-$ groups are presented in Fig. 2A. The result of the log-rank test was $P < 0.01$. The adjusted Cox proportional hazard analysis, which was adjusted for gender and age, also showed that the ASA status was associated with the mortality rate of the IIM-ILD patients [positive ASA *vs* negative ASA, hazard ratio (HR) 0.45 (0.26–0.79), $P = 0.005$].

A total of 241 patients with IIM-ILD and MDA-5 antibodies were divided into two groups based on their MDA-5 antibody detection results, including the MDA-5$^+$-IIM-ILD group ($n = 91$) and MDA-5$^-$-IIM-ILD group ($n = 150$). The MDA-5$^+$ patients had a higher mortality rate [33.0 *vs* 15.3%, respectively; OR 2.72, 95% CI: 1.46, 5.06]. The Kaplan–Meier curves for mortality in the anti-MDA-5$^+$ group and anti-MDA-5$^-$ groups are presented in Fig. 2B. The result of the log-rank test was also $P < 0.01$. The adjusted Cox proportional hazard analysis, which was adjusted for gender and age, also showed that the anti-MDA-5 status was associated with the mortality rate of the IIM-ILD patients [positive MDA-5 antibody *vs* negative MDA-5 antibody, HR 2.87 (1.65–5.05), $P < 0.001$].

The patients were divided into the following four subgroups based on both ASA and MDA-5 antibody results:

FIG. 2 Kaplan–Meier survival curves of IIM-ILD patients with different statuses of the myositis specific antibodies



(**A**) Kaplan–Meier survival curves of idiopathic inflammatory myopathy-interstitial lung disease (IIM-ILD) patients with different statuses of the anti synthetase antibody (ASA) [ASA-positive (ASA^+) IIM-ILD, $n = 157$; ASA-negative (ASA^-) IIM-ILD, $n = 147$]: ASA^- patients had a significantly lower survival rate than did those with ASA^+ IIM-ILD (log-rank, $P = 0.003$). (**B**) Kaplan–Meier survival curves of IIM-ILD patients with different statuses of the anti-melanoma differentiated-associated protein-5 antibody (MDA-5) [MDA-5-negative ($MDA\text{-}5^-$) IIM-ILD, $n = 150$; MDA-5-positive ($MDA\text{-}5^+$) IIM-ILD, $n = 91$]: $MDA\text{-}5^+$ patients had a significantly lower survival rate than did those with $MDA\text{-}5^-$ IIM-ILD (log-rank, $P = 0.001$).

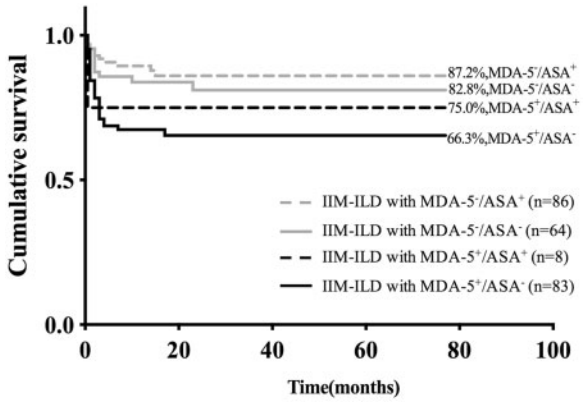
$MDA5^+/ASA^+$-IIM-ILD (8 cases), $MDA5^+/ASA^-$IIM-ILD (83 cases), $MDA5^-/ASA^+$-IIM-ILD (86 cases) and $MDA5^-/ASA^-$IIM-ILD (64 cases). The mortality rates in the four groups were 25.0, 33.7, 12.8 and 17.2%, respectively. The Kaplan–Meier curves for mortality in these groups are presented in Fig. 3. The adjusted Cox proportional hazard analysis, which was adjusted for gender and age, also showed that the combined ASA and anti-MDA-5 statuses were associated with the mortality rate of the IIM-ILD patients [$MDA5^+/ASA^-$ *vs* $MDA5^-/ASA^-$, HR 1.49 (1.06–2.11), $P = 0.02$; $MDA5^+/ASA^-$ *vs* $MDA5^-/ASA^+$, HR 1.55 (1.22–1.97), $P < 0.001$; $MDA5^+/ASA^-$ *vs* $MDA5^-/ASA^+$, HR 1.89 (0.39–9.27), $P = 0.43$]. The prognosis of patients with $MDA5^+/ASA^-$-IIM-ILD was the worst.

Discussion

With the extensive application of myositis autoantibody profiling in clinical practice, ASA has been increasingly recognized to occur in ILD patients with IIM, and patients with $MDA\text{-}5^+$ are susceptible to rapidly progressive ILD, which seriously affects their prognosis. In this study, we analysed the prognosis of patients with IIM-ILD across clinical IIM subgroups and two MSA statuses, i.e. ASA and MDA-5 antibodies. We found that the prognoses of DM and CADM were worse than that of PM, and the prognoses of DM-ILD and CADM-ILD were worse than that of PM-ILD; ASA^+-IIM and $MDA\text{-}5^+$-IIM cases were more likely to develop ILD, whereas the presence of ILD among the Jo-1-ASA^+-IIM and non-Jo-1-ASA^+-IIM groups did not significantly differ. The presence of ILD did not affect the prognosis of patients with ASA^+-IIM, while patients with $MDA\text{-}5^+$ IIM-ILD demonstrated the worst prognosis regardless of the ASA positivity. To the best of our knowledge, this study is the largest prognostic analysis to simultaneously consider both the traditional clinical subtypes and clinical-serological patterns of IIM-ILD.

Patients with IIM and certain demographic and clinical characteristics are more likely to be complicated with ILD.

FIG. 3 Kaplan–Meier survival curves of IIM-ILD patients with different statuses of the ASA and MDA-5



(**1**) Anti-melanoma differentiated-associated protein-5 antibody (MDA-5)-negative and anti synthetase antibody (ASA)-positive (MDA-5$^-$/ASA$^+$) idiopathic inflammatory myopathy-interstitial lung disease (IIM-ILD), $n = 86$; MDA-5-negative and ASA-negative (MDA-5$^-$/ASA$^-$) IIM-ILD, $n = 64$; MDA-5-positive and ASA-positive (MDA-5$^+$/ASA$^+$) IIM-ILD, $n = 8$; MDA-5-positive and ASA-negative (MDA-5$^+$/ASA$^-$) IIM-ILD, $n = 83$. (**2**) MDA-5$^+$/ASA$^-$ IIM-ILD patients had significantly lower survival rates than did those with MDA-5$^-$/ASA$^+$ and MDA-5$^-$/ASA$^-$ IIM-ILD (log-rank, $P < 0.001$ and $P = 0.02$, respectively). (**3**) There was no significant difference in the survival time between MDA-5$^+$/ASA$^-$ and MDA-5$^+$/ASA$^+$ IIM-ILD patients (log-rank, $P = 0.43$).

For example, an IIM analysis conducted in the UK showed that patients of African descent were more likely to develop ILD than were Caucasian patients, and patients with high creatine kinase and ESR values, concurrent with joint diseases and capillary nailfold loops, were also more likely to develop ILD. However, age, sex, clinical subtype of IIM and course of IIM were not associated with the presence ILD in patients with IIM [10]. Previous studies have reported that the prognosis of Caucasian patients with IIM is relatively positive, likely because of the ethnicity, clinical phenotype and therapeutic response of these IIM [11, 12]. Many Asian studies have reported that the presence of ILD in patients with MDA-5$^+$ is 92–100%, whereas reports from Europe and the USA have indicated that ILD rates in patients with MDA-5$^+$-IIM are only 50–73% [13]. In our study, the presence of ILD differed by IIM subtype. The CADM group showed the highest incidence of ILD, followed by the DM group, and the PM group had the lowest presence of ILD. The MDA-5 positivity rate in this study was 30.8%, whereas the presence of ILD among patients with MDA-5$^+$ IIM was 97.9%, which was much higher than that among MDA-5$^-$-IIM cases (71.3%).

In recent years, with the improvement of immunosuppressant and other therapies, the prognosis of IIM has significantly improved [14]. However, ILD is still a very important risk factor, affecting the prognosis of IIM [14–19]. Our study also showed that the prognosis of IIM-ILD patients was significantly worse than that of IIM patients without ILD. The study by Yamasaki *et al.* from Japan [16] showed that ILD was the main cause of death in DM and CADM patients, and ILD was one of the independent risk factors affecting the prognosis of IIM patients. Therefore, improving the prognosis of ILD may improve the prognosis of IIM patients. The prognosis of ILD associated with different clinical subtypes of IIM is also different. In this study, the prognoses of DM-ILD and CADM-ILD were worse than that of PM-ILD. Several IIM-ILD analyses in Japan showed similar results [16, 18, 20]. Moreover, similar to the study by Sato *et al.* [18], male sex and an onset age of no less than 50 years are also independent risk factors associated with the death of IIM patients in this study.

With the further application of myositis autoantibody profiling in clinical practice, it has been found that some MSAs are related to the incidence of ILD, such as ASA and MDA-5 [1, 10, 21–23]. In this study, the rate of ILD among patients with ASA$^+$ or MDA-5$^+$ was significantly higher than that who tested negative for these autoantibodies. In this study, eight cases with concurrent ASA$^+$ and MDA-5$^+$ were found to have ILD (100%). Some studies have proposed that the presence of ILD is varied across different subtypes of ASA, and the presence of ILD in the non-Jo-1-ASS-IIM group was higher than that in the Jo-1-ASS-IIM group [23–25]. However, no difference was found regarding the presence of ILD between the Jo-1-ASS and non-Jo-1-ASS groups in this study, nor was the Jo-1 antibody a prognosis-related factor among ASS cases. Additional statistical analyses showed that an onset age of >50 years, tumour presence and mediastinal/subcutaneous emphysema were independent risk factors for death among the ASS group, whereas concurrent ILD, mechanic's hand and Jo-1 antibody were not associated with a poor prognosis among these patients (i.e. although the presence of ILD was higher in the ASS group than the non-ASS-IIM group, the concurrence of ILD was not associated with a prognosis). Moreover, many reports have showed that the prognosis of patients with Jo-1-ASS is better than that of those without Jo-1-ASS [26–28], which suggests that the difference in prognosis is related to the different presence of ILD, the difference in initial pulmonary function and delayed treatment due to a lack of understanding of non-Jo-1-ASS-ILD [28, 29]. Rojas *et al.* [28] did not identify factors related to the different prognosis between Jo-1-ASS and non-Jo-1-ASS patients through an in-depth analysis. A meta-analysis by Lega *et al.* (27 studies, $n = 3{,}487$) showed that although the presence of ILD among non-Jo-1-ASS patients was higher than that among Jo-1-ASS patients, no significant difference was found with regard to mortality between the two subgroups, which matches the results of our study [23].

It is well known that MDA-5 antibody positivity is an indicator of poor prognosis of IIM and IIM-ILD [13, 18, 30]. The prognosis analysis of 93 patients who were MDA-5$^+$ in this study also confirmed that the prognosis of MDA-5$^+$ patients was worse than that of MDA-5$^-$

patients. The follow-up regression analysis showed that only an onset age of no less than 50 years old was an independent risk factor for death in MDA-5$^+$ patients, and the classical skin lesions were a relatively good prognostic index in these patients. The meta-analysis by Li *et al.* [31] showed that MDA-5 antibody is correlated with skin lesions, such as Gottron's sign or papules, mechanic's hand, V rash, skin ulcers, panniculitis and alopecia. Therefore, MDA-5$^+$ patients are prone to skin lesions, and once the classical skin lesions associated with DM occur, patients actively seek medical advice from the fields of dermatology, rheumatology, immunology and general internal medicine, which may result in early detection, early diagnosis, early treatment and even improvement in the prognosis of MDA-5$^+$-IIM patients [13]. However, patients without classic skin lesions associated with dermatomycosis may experience delayed diagnosis and treatment of the disease due to neglect by the patients and dermatologists, and patients may visit the respiratory department or emergency room only when obvious dysponea or even respiratory failure occurs, thus missing the opportunity to receive early treatment.

Although ILD is not a prognosis-related index of ASS patients, similar to the report by Hozumi *et al*. [32], the subgroup analysis in this study showed that for IIM-ILD, the prognosis of ASA$^+$ patients was better than that of ASA$^-$ patients, i.e. ASA positivity may affect the prognosis of IIM-ILD patients. However, the group of ASA$^-$ patients included some MDA-5$^+$ patients; therefore, to further determine whether ASA and MDA-5 antibodies affect the prognosis of IIM-ILD patients, this study further divided IIM-ILD patients into four subgroups, namely, ASA$^+$/MDA-5$^-$, ASA$^+$/MDA-5$^+$, ASA$^-$/MDA-5$^+$ and ASA$^-$/MDA-5$^-$. The results showed that regardless of ASA positivity, MDA-5$^+$ patients had the worst prognosis, and ASA positivity was not a prognostic factor for MDA-5$^-$-IIM-ILD patients, which further confirmed that MDA-5$^+$ is an indicator of poor prognosis in IIM and IIM-ILD patients [13, 18, 30]. Isoda *et al.* compared the prognosis of IIM-ILD patients with different combinations of ASA and MDA positivity and found that in terms of the 2-year survival rate, the prognosis of the ASA$^-$/MDA-5$^+$ group ($n = 11$) was worse than those of the ASA$^+$/MDA-5$^-$ group ($n = 12$) and the ASA$^-$/MDA-5$^-$ group ($n = 11$) [33]. Most MDA-5 patients died within 6 months after diagnosis, and there was no significant difference in mortality between 25 weeks and 2 years after diagnosis. Therefore, it is suggested that myositis autoantibody profiling should be performed as early as possible for IIM-ILD patients to identify the clinical-serological types, to fully recognize the true prognosis-related indicators and to initiate individualized treatment as early as possible. However, the positivity of serum anti-MDA-5, and the clinical phenotype of MDA-5$^+$-IIM are varied from different races, e.g. Eastern Asians (Japanese and Chinese) *vs* Caucasians. The positivity of anti-MDA-5 was only 1.2% in Betteridge's study [34], but it was 12.5% in Li's study [35]. The different genetic characters and the different tests for anti-MDA-5 might causes the difference. We look forward to a nationwide and even global multicentre clinical study similar to that conducted by Kamiya *et al.* [36,37] to further clarify the prognosis-related indicators of IIM-ILD.

There were several limitations of our study. First, all patients were admitted to a tertiary hospital, which could lead to selection bias. Second, it was a retrospective study, and myositis autoantibody profiling was not performed routinely for every enrolled patient; therefore, the effect of autoantibody status on prognosis could not be analysed accurately. Third, the patients were transferred from different departments. Although most patients were treated with CS combined with immunosuppressants, the specific treatment regimens (e.g. the CS protocols and immunosuppressant treatments) were not consistent.

Conclusion

The prevalence of ILD in IIM and the prognosis of IIM-ILD patients may vary depending on the statuses of ASA and MDA-5 antibodies, Therefore, a targeted clinical/serological approach is suggested for the identification of IIM-ILD cases, especially to assess ASA and MDA-5 antibody statuses.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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